stepped-up dosage scheme such that infusion-related reactions associated with full dosing are at least substantially avoided.

15. The method of claim 14, wherein said antibody binds to CD20.

16. The method of claim 15, wherein said antibody is a chimeric antibody.

17. The method of claim 16, wherein said antibody is RITUXAN®.

18. The method of claim 17, wherein said antibody is administered at an initial dose of 100 $mg/_{m2}$, and the remainder of a 375 $mg/_{m2}$ dose is administered on the following day.--

REMARKS

This amendment is responsive to the Office Action dated February 29, 2000. Entry of the foregoing and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 CFR § 1.112, are respectfully requested.

The application has been amended above. In particular, the specification has been amended to correct trademark designations as requested in the Office Action. Furthermore, the trademark "RITUXIMAB®" has been replaced with the trademark "RITUXAN®" in order to maintain consistency and avoid confusion. These trademarks refer to the same

product and Applicants would be willing to submit a declaration in this regard if the Examiner deems it necessary.

The specification has also been amended to refer to the most recent address for the ATCC as requested in the Office Action. In addition, the hyperlink on page 15 ("http://www.cancernetwork.com") has been replaced by citation to publications that were available in the art at the time the present application was filed and which report the same findings for which the website was cited. A comparison of the reference abstracts and the website article, both attached hereto, confirm that the references teach the same parameters of Fludarabine treatment as does the website. No new matter has been added.

The amendments to pages 9-10 of the specification serve to correct typographical errors in the data reported in the specification. The fact that these amendments correct mere typographical errors would be clear to one of ordinary skill in the art upon reading the specification, and therefore the corrections do not constitute new matter. For instance, it is clear in the context of the entire passage on page 9 (especially page 9, line 18) that all instances of "10^3L" should really be 10^9/L, and the skilled artisan would clearly recognize this to be the case given the normal range of white blood cell counts known in the art. Likewise, it is clear in context that the post-treatment range of 37-24.6 reported on line 15 should actually be 3.7-24.6 (x 10^9), particularly given that the mean is reported as 11 x 10^9 (page 9, line 14). Also, it is apparent that the letters "Sn" in Sn x 10^9/L on page 9, line 18, should have been a mean number between the range of 2 to 120. This passage should have read "56 x 10^9/L" and has been corrected accordingly. Applicants would be happy to submit a declaration as well as further documentation to verify that these corrections are minor typographical errors if the Examiner believes this would be necessary. No new matter has

been added by any of these amendments, particularly given that they constitute only corrections of observed results rather than treatment parameters necessary for practice of the invention.

The claims have also been amended in response to the Office Action. For instance, claims 1 and 12 have been amended to clarify that "fragment" means "antigen binding fragment", as suggested in the Office Action at the bottom of page 8. Claims 1 and 12 have also been amended to recite positive process steps that give meaning to the phrase "therapeutically effective" as suggested in the Office Action at page 9. In particular, the claims have been amended to indicate that a therapeutically effective amount is effective to reduce the number of circulating tumor cells. This amendment finds support on page 13, line 10, and on page 9, lines 12-14. No new matter has been added.

Claim 8 was amended to a Markush format so that the term "and/or" could be deleted, and also in order to clarify the purpose of the lymphokine combination treatment. Support for this amendment may be found in Example 4, on page 13. Claim 11 was amended to specify the therapeutic agents included in COP and CHOP regimens. Support for this amendment may be found on page 8, second full paragraph. Finally, new Claims 13-18 were added. Claim 13 finds support in original Claims 1 and 3, and in the specification at page 3, lines 5-8. Claims 14-18 are directed to a novel finding reported in the specification, that being that the toxicity associated with administration of therapeutic antibodies can be avoided or reduced by utilizing a stepped up dosing scheme. Support for these claims may be found in Example 1 of the specification. No new matter has been added.

Turning now to the Office Action, it is first noted that trademarks should be capitalized wherever they appear and should be accompanied by generic terminology.

Applicants have reviewed the specification and capitalized all trademark designations that were not already capitalized. Applicants also found generic descriptions of RITUXAN® (which is the same as RITUXIMAB®) at page 6, lines 5-6, and of PRIMATIZED® at page 5, lines 4-5. Thus, it appears that all uses of trademarks are in accordance with proper practice.

Next, the disclosure is objected to because it contains the incorrect address of the ATCC. Applicants have amended the specification to refer to the most recent address of the depository. Therefore, this objection has been rendered moot.

The disclosure was also objected to for containing an embedded hyperlink for an internet website on page 15. Applicants have amended the disclosure to refer to publications known in the art at the time that teach the same information as contained on this website. So that the Examiner may confirm that the information contained on the website and in the cited references is in fact the same, Applicants attach hereto a copy of the website material referenced at page 15, as well as copies of the reference abstracts. Withdrawal of the objection is respectfully requested.

Claim 7 was rejected under 35 U.S.C. §112, first paragraph, for failing to provide an adequate description of the invention because the disclosure allegedly fails to include evidence of the deposit of the CHO cell transfectoma that secretes RITUXAN®. To correct this deficiency, the Examiner requests an affidavit by Applicant or Applicants' counsel affirming that restrictions upon public access to the deposits will be removed upon the grant of an application. Applicants respectfully submit that the specification has been amended above to refer to the ATCC number assigned to the deposit, that it is clear by the disclosure at page 6 that this cell line was deposited, and moreover that restrictions on public access were irrevocably withdrawn upon issuance of U.S. Patent 5,736,137 which has the same assignee

as the present application. Applicants respectfully submit that no more is required to satisfy the deposit rules, and that this rejection should be withdrawn.

Next, Claims 1-12 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to enable the full scope of the claimed invention. Essentially, the Examiner believes that anti-CD20 antibodies other than RITUXAN® may have different structural and functional properties, and that the specification is allegedly silent with regard to what specificity and affinity would be necessary for antibodies of the claimed immunotherapy. The Examiner also states that the specification has not taught how one skilled in the art would make the necessary chimeric, humanized or human antibodies as to avoid an immune response against the foreign antibodies, and further that the specification has not taught what adjuvants or dosages would be appropriate for the claimed method. The Examiner further alleges that there is insufficient guidance and/or working examples in view of the unpredictability of immunotherapeutics in general to justify the scope of the claims. Applicants respectfully traverse this rejection.

Applicants respectfully submit that even though antibodies directed to the same antigen might have different affinities and functional characteristics, one of skill in the art could readily identify an antibody that binds to CD20 with similar affinity and specificity as does RITUXAN® using techniques that are well known in the art. Indeed, U.S. Patent 5,736,137, issued April 7, 1998, claims an immunologically active, chimeric anti-CD20 antibody produced from the transfectoma that produces RITUXAN®. With that knowledge in hand, the skilled artisan could readily produce anti-CD20 antibodies using similar techniques, and screen such antibodies for those having an affinity and functional activity

similar to RITUXAN®. They would only need the motivation to do so, which the present invention provides.

Indeed, the novelty of the presently claimed invention does not lie in an anti-CD20 antibody per se. Rather, a novel aspect of the presently claimed invention lies in the revelation that anti-CD20 antibodies can be used to treat hematological malignancies, which would not have been expected given the low expression of CD20 on these cells and the high numbers of circulating tumor cells characteristic of these disorders.

The antibodies to be used for the claimed immunotherapy were described in detail in U.S. Patent 5,736,137, which was incorporated by reference into the present application on page 6. Given that the enablement requirement may be satisfied by the general incorporation by reference of a U.S. patent in an applicant's specification, and that U.S. Patent 5,736,137 describes the isolation, screening and characterization of RITUXAN® in such detail that similar antibodies could readily be identified, no further description of anti-CD20 antibodies is required. *See* Ex Parte Raible, 8 USPQ 2d 1709, 1710 (PTO Bd App & Int 1988) (discussing how incorporation by reference of a U.S. Patent is sufficient to indicate what is likely to be known by persons of ordinary skill in the art).

The Office Action also alleges that the specification is silent with regard to what specificity and affinity would be necessary for antibodies of the claimed immunotherapy (page 6, five lines from the bottom). Applicants respectfully note that the specification defines the preferred antibody at page 4, last paragraph, as one that binds CD20 with an affinity ranging from 10^{-5} to 10^{-9} M. Moreover, it is clear from the disclosure that the specificity must be such that antibody therapy results in a reduction of circulating tumor cells.

Thus, the affinity and specificity of the antibodies to be used in the present invention are made clear in the disclosure.

The Office Action further states that the specification has not taught how one skilled in the art would make the necessary chimeric, humanized or human antibodies as to avoid an immune response against the foreign antibodies. However, at page 5, fourth paragraph, the specification states that methods for producing chimeric, primate, PRIMATIZED®, humanized and human antibodies are well known in the art, and moreover several patents disclosing the requisite technology are incorporated by reference. Again, the novelty of the presently claimed invention does not lie in a method of making therapeutic antibodies (although antibodies to be designed in the future for use in the claimed methods would certainly be encompassed). Rather, the presently claimed invention concerns the use of such antibodies for the treatment of hematological malignancies and particularly for the treatment of CLL, B-PLL and traditional non-Hodgkin's lymphoma.

The Office Action next alleges that the specification has not taught what carrier or adjuvant would be appropriate for the "passive" immunotherapy, and what dosages would be effective for the prevention and/or treatment of a hematological malignancy. This statement also is unfounded given the disclosure at page 7, first two full paragraphs, where appropriate pharmaceutical carriers are disclosed, and effective doses are disclosed (with the caveat that an effective dose will depend on the particular antibody, but that optimization would not required undue experimentation).

The references in the Office Action to "passive" immunotherapy, adjuvants and methods of prevention are somewhat puzzling. The present claims are directed to methods of treating hematological malignancies, not vaccinating against them. Applicants fail to

understand why adjuvants would be required for the claimed methods which begs the question as to why such adjuvants must be disclosed. The presently claimed methods target disease which is already in progress and in this sense the methods are active immunotherapy. Indeed, while you might administer an anti-CD20 antibody to a patient who has undergone successful treatment as a follow-up step and a means of ensuring the disease does not return it makes no sense to deplete healthy patients of their B-cells as a means of preventing leukemic diseases. Accordingly, the fact that the application does not disclose parameters as to how to employ anti-CD20 antibodies in the passive sense is of no consequence.

Finally, the Office Action alleges that there is insufficient guidance and/or working examples in view of the unpredictability of immunotherapeutics in general to justify the scope of the claims. However, the specification provides at least two examples which report data from *in vivo* trials to illustrate the efficacy of the antibody treatment for patients suffering from hematological malignancies. Given that the Federal Circuit has held that a disclosure cannot be found lacking for the mere failure to disclose a working example, Applicants fail to understand why the disclosure of at least two working examples is insufficient to meet the enablement requirement of §112, first paragraph. *See,* e.g., Ex Parte Nardi & Simier, 229 USPQ 79, 80 (Bd. App. 1986) ("Absence of working example in specification is without significance, since examples are not necessary").

For instance, Example 1 of the subject specification reports the treatment of four patients diagnosed with either B-PLL, CLL or transformed non-Hodgkins, all of whom had elevated leukocyte counts as a result of blood tumor involvement. Treatment with RITUXAN® resulted in "a rapid decrement in circulating tumor cell load" from a pretreatment mean of 98 X 10^9 to 11 X 10^9/L (page 9). Similarly, as reported in Example 3,

of eight patients diagnosed with CLL and treated with RITUXAN®, one achieved a full remission and all others but one experienced a reduction in peripheral blood lymphocytosis.

Thus, Applicants respectfully submit that disclosure may be found in the specification for all items which the Examiner has alleged were missing and are allegedly required for the specification to enable the presently claimed methods. Most of these items, i.e., methods of making antibodies, methods of screening for antibodies having a certain affinity and activity, and types of pharmaceutical carriers, were known in the art at the time the present invention was filed and could be readily employed by those of skill in the art in practicing the claimed methods. While other items such as appropriate dosage ranges might be unique to the present invention, acceptable ranges are provided to guide those of skill in the art in the practice of the invention. Moreover, dosages would be expected to vary in any immunotherapeutic method, and optimization of the appropriate dose based on the guidance provided in the specification would not require undue experimentation. Finally, Applicants report not just one but two working examples showing actual *in vivo* data demonstrating the efficacy of anti-CD20 antibodies for the treatment of hematological malignancies associated with a high number of circulating tumor cells. In view of all these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

As a separate issue, at the bottom of page 8 of the Office Action, the Examiner notes that the recitation of "fragment" is impermissible in scope because it reads on fragments that do not bind to the antigen. The Examiner indicated that Applicants could obviate the particular ground for rejection by amending the claims to read "antigen-binding" fragment. Applicants have followed the Examiner's suggestion, therefore this rejection should now be withdrawn.

Claims 1 and 12 were separately rejected under 35 U.S.C. § 112, first paragraph, because they are broadly directed to administering a "therapeutically effective amount," whereas the claims do not recite an endpoint indicative of anticipated results to give meaning to this phrase. In response thereto, Applicants have added a positive process step to Claims 1 and 12, whereby it is now clear that a "therapeutically effective amount" results in a reduction of circulating tumor cells. Accordingly, this rejection should now be withdrawn.

Next, Claims 1-12 were rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. The particular grounds for the rejection will be addressed in the order presented in the Office Action for the convenience of the Examiner.

First, Claims 1 and 12 were rejected for not including method steps or a resolution step. In addition, the claims were rejected because they do not state what function is to be achieved by an "effective amount." As discussed above, these claims have been amended to include a positive process step which relates back to the preamble. This amendment renders both grounds for the rejection moot, and they should now be withdrawn.

Claims 1 and 12 were also rejected for the phrase "fragment thereof" because it is unclear what portion of the antibody such a fragment would encompass. As discussed above, the claims have now been amended to clarify that "antigen-binding" fragments are intended. Accordingly, this ground for the rejection should now be withdrawn.

Claim 1 was also rejected for using the phrase "high numbers" because it is allegedly impossible to determine the metes and bounds of such a phrase. Applicants respectfully traverse and note that this phrase must be read in the context of a hematological malignancy, as mentioned in the preamble of the Claim, and so long as it is read in context, the meaning of the phrase "high numbers of circulating tumor cells" would be clear to one of skill in the

art. Indeed, this phrase has a well understood meaning to those familiar with hematological disorders, as evidenced by the materials attached to this Reply.

For instance, according to the website of TIRGAN Oncology Associates, CLL is diagnosed by the presence of an "elevated" white blood cell count. In fact, the beginning stages of CLL are characterized by what is described as a "high white blood count." According to the drkoop.com site, a normal white blood cell count generally ranges from 4,500 to 10,000 cells per microliter (with 1500-4500 of that range being lymphocytes). So it is clear that a high white cell count will be higher than the normal lymphocyte range, given what is known about the characteristics of CLL. This is in accordance with the mean pre-treatment and mean post-treatment ranges reported in Example 1 of the specification, where RITUXAN® therapy resulted in a rapid decrement of tumor load.

It is well-established that claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art. In re Sneed & Young, 218 USPQ 385, 388 (Fed. Cir. 1983). While one skilled in the art would understand the claim language when read in light of the specifications, as the claims must be, those claims are sufficiently definite for purposes of 35 U.S.C. § 112, second paragraph. Rosemont Inc. v. Beckman Instruments, Inc., 221 USPQ 1,7 (Fed. Cir. 1984). It is clear from the attached materials that those skilled in the art are aware of what constitutes a high number of white blood cells, and that such high numbers may be used as an indication of a hematological malignancy.

Applicants acknowledge that the phrase "high numbers" is one of degree, and may read on a range of numbers. Nevertheless, the Federal Circuit has noted that when a word of degree is used, it is not necessarily indefinite. Rather, the Office must determine whether the patent's specification provides some standard for measuring that degree, and whether one of

ordinary skill in the art would understand what is claimed when the claim is read in light of the specification. Seattle Box Co., Inc. v. Industrial Crating & Packing, Inc., 221 USPQ 568, 574-5 (Fed. Cir. 1984). Seeing as the specification discloses a pretreatment range of circulating tumor load and the "normal" ranges of white blood cells and lymphocytes are well known in the art, one of skill in the art would clearly understand what is meant in the claims by the phrase "high numbers." However, applicants would gladly submit a declaration in addition to the attached documentation if preferred by the Examiner. Reconsideration and withdrawal of this ground for the rejection is respectfully requested.

Next, Claim 4 was rejected for reciting "chimeric," because the Examiner believes that the exact meaning of this term is unknown, and that there is no definition of this term in the specification. Applicants respectfully submit that there is indeed a definition of this term at page 5, lines 1-3, where a chimeric antibody is defined as one having non-human variable regions and human constant regions. Accordingly, the definition of "chimeric" is clear from the specification and this rejection should be withdrawn.

Next, Claim 8 was rejected because it was allegedly unclear if the "and/or" terminology denoted a Markush group. In response thereto, Applicants have amended the claim so that it uses appropriate Markush group language. Withdrawal of this rejection is respectfully requested.

Claim 11 was rejected because the identity of the abbreviations COP and CHOP are allegedly not well known in the art. Applicants respectfully traverse and point to the attached copy of the cancernetwork website as evidence that these abbreviations are in fact well known in the art. Nevertheless, the claim has been amended to recite each of the components

of the COP and CHOP regimens. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1, 4, 7, 8, 11 and 12 were rejected under 35 U.S.C. §102(b) because they are allegedly anticipated by Maloney et al. (hereafter "Maloney"). Essentially, it is the Examiner's opinion that Maloney discloses a hematologic malignancy associated with high numbers of circulating tumor cells that is refractory to chemotherapy by administering a therapeutically effective amount of an anti-CD20 antibody in combination with the chemotherapeutic agent, prednisone.

Applicants respectfully traverse in view of the clarification of the definition of "high numbers" above, and in view of the fact that the reference specifically states at page 2193, column 2, last full paragraph, that patients with CLL and those having more than 5000 lymphocytes per microliter were excluded from the reported trial. Even if the Examiner believes that "high numbers" reads on the disclosure of Maloney (which Applicants strenuously traverse seeing as 5000 lymphocytes per microliter is above the normal range for lymphocytes, which is 1500-4500), Maloney would not anticipate a claim directed specifically to B-PLL or CLL, or to transformed non-Hodgkin's lymphoma. Accordingly, the limitations of Claims 1 and 3 have been united in new Claim 13 for the purpose of expediting prosecution. Withdrawal of the rejection is respectfully requested.

Claims 1-4, 7, 8, 11 and 12 were rejected under 35 U.S.C. §102(a) as being anticipated by Ford and Donegan. According to the Office Action, Ford and Donegan allegedly disclose a method of treating a hematological malignancy associated with high numbers of circulating tumor cells, and in particular CLL, by administering a therapeutically

effective amount of RITUXAN® in combination with chemotherapy. Applicants respectfully traverse this rejection.

Upon a review of the reference, it is clear that the only detailed study reported in Ford and Donegan involved the treatment of indolent non-Hodgkin's B-cell lymphoma, not CLL. With regard to CLL, the only mention is non-enabling, and indicates that a study had been *initiated* to evaluate RITUXAN® *in combination* with chemotherapy. The skilled artisan would not have believed or expected, based on this report, that RITUXAN®, either alone or in combination with other treatments, would be effective for CLL because of the very high numbers of circulating tumor cells, and the fact that CLL cells typically do not express CD20 at the high density which is characteristic of B-cell lymphomas. The surprising nature of these results is emphasized in the specification at the paragraph bridging pages 3-4, and serves as a persuasive reminder as to why a non-enabling disclosure may not serve as anticipatory prior art.

For instance, the only mention in Ford and Donegan as to the treatment of CLL using RITUXIMAB® is on page 48, column 2, where it is disclosed that a study had recently been initiated to "evaluate different schedules" using combination chemotherapy plus RITUXIMAB® in CLL. It is not disclosed, however, whether such treatment is successful, what schedules are to be tested, what dosages of RITUXIMAB® are to be used in combination therapy, what chemotherapy regimens are to be used at what dosages, and it is certainly not even suggested that RITUXIMAB® might be successful when administered alone. In fact, the skilled artisan upon reading such a disclosure would not have believed such a study would be successful given the lower density of CD20 on the surface of CLL cells, and the fact that CLL is associated with high numbers of circulating tumor cells.

The Federal Circuit has held that a non-enabling disclosure, "imperfect and never perfected will not serve as an anticipation or as part of the prior art, for it has not served to enrich it." Fromsen v. Advance Offset Plate, Inc. 225 USPQ 26, 33 (Fed. Cir. 1985). The PTO Board of Appeals has agreed, noting that "it is axiomatic that a reference itself must have an enabling disclosure to be used as a proper reference." Ex parte Gould, 231 USPQ 943, 945 (PTO Bd. App. & Int. 1985). Because the Ford and Donegan reference cited in the Official Action discloses neither the means to achieve treatment nor the positive results that are necessary to convince those of skill in the art in view of the unexpected nature of the invention, Ford and Donegan is not a proper §102 reference.

Thus, given that Ford and Donegan do not disclose a method of treating CLL with RITUXAN®, alone or in combination with other therapies, and do not enable, anticipate or render obvious the same, reconsideration and withdrawal of this rejection is respectfully requested. Applicants would be glad to submit a §1.131 declaration antedating the Ford and Donegan reference if the Examiner so requires, although applicants do not believe this is necessary given the above arguments.

Next, Claims 1, 5, 6 and 9 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over the combination of Ford and Donegan and Maloney. In the Examiner's opinion, although the doses recited in dependent Claims 5 and 9 are not specifically disclosed in the references, they would be allegedly obvious to one of ordinary skill in light thereof, and one of ordinary skill would have been motivated to use these doses with a reasonable expectation of success given that dosages of any therapeutic agent must be adjusted and optimized. Applicants respectfully traverse this rejection.

First, as discussed above, patients with high numbers of circulating tumor cells were specifically excluded from the trial reported in Maloney, therefore no motivation to treat CLL and other hematological malignancies using anti-CD20 antibodies can be gleaned from this reference. This deficiency is not rectified by Ford and Donegan because Ford and Donegan report only a non-enabling disclosure concerning the possible treatment of CLL with both RITUXAN® and a chemotherapeutic agent.

Furthermore, as discussed in the specification at the paragraph bridging pages 3 and 4, the discovery that RITUXAN® administered alone is effective for treating hematological malignancies such as CLL is surprising notwithstanding the success of RITUXAN® in the treatment of non-Hodgkin's lymphoma, given the very high numbers of circulating tumor cells known to be associated with CLL, and the fact that CLL cells do not express CD20 at a density comparable to the cells of other malignancies. These factors together render the claimed immunotherapy method in general novel and non-obvious, therefore any particular dosage would also be novel and non-obvious given that the skilled artisan would not be motivated to try let alone optimize. For these reasons, reconsideration and withdrawal of the rejection is respectfully requested.

Finally, Claims 1, 8 and 10 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Ford and Donegan or Maloney in view of Hudziak et al. In the Examiner's opinion, although neither Ford and Donegan nor Maloney teach the administration of RITUXAN® in combination with a lymphokine, it would have been *prima facie* obvious to do so in view of the disclosure in Hudziak of the simultaneous administration of therapeutically effective amounts of antibodies along with therapeutically effective amounts of cytokines such as TNF-alpha, and the teaching in Hudziak that cytotoxic factors such as

TNF-alpha exert a cytostatic or cytotoxic effect towards circulating tumor cells. Applicants respectfully traverse this rejection.

First, Applicants reiterate the above points that neither Maloney nor Ford and Donegan anticipate or render obvious the use of anti-CD20 antibodies alone for the treatment of CLL. Since Hudziak does not make up for this deficiency, the cited combination cannot be said to render obvious the claimed combined treatment. Moreover, Hudziak's purpose for administering cytokines differs from that of the present invention, wherein cytokines are used for the purpose of upregulating the CD20 molecule on the surface of tumor cells in order to enhance the effects of the therapeutic anti-CD20 antibody.

In contrast to the present invention, Hudziak uses cytokines for the purpose of destroying malignant tumor cells. One of skill in the art would not be motivated to combine the use of cytokines and anti-CD20 antibodies if cytokines alone could be used to destroy the tumor cells. This is particularly true given the low level of expression of CD20 on CLL cells, where a cytokine administration regimen that results in suppression of cell growth would be expected to decrease the efficacy of an anti-CD20 antibody rather than enhance its therapeutic efficacy, i.e., by rendering the cells unresponsive to antibody treatment for a period of time. In fact, Hudziak actually teaches away from the present invention in that it suggests that cytokines alone would weaken tumor cells. Accordingly, one would not expect that such cells would increase the expression of CD20 thereby becoming more responsive to antibody therapy.

Given that the references when taken alone or in combination fail to render obvious the claimed invention, and in fact the teachings of Hudziak lead one away from a combined

therapeutic regimen which includes the administration of cytokines, reconsideration and withdrawal of this rejection is respectfully requested.

In view of the above amendments and remarks, this application is believed to be in allowable condition. If there are any questions regarding this amendment and response, or with the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the present application may be expedited.

Respectfully submitted,

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